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Non-covalent synthesis of organic nanostructures *

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Abstract: This review describes the synthesis, characterization and functionalization of hydrogen bonded, box-like assemblies. These assemblies are formed upon mixing bismelamine calix[4]arenes with a complementary barbiturate in apolar solvents. Various techniques for the characterization have been used, like ^{1}H NMR spectroscopy, X-ray crystallography and a novel MALDI-TOF MS technique. The use of cyanurates instead of barbiturates results in the formation of three conformational isomers. The ratio in which these assemblies are formed depends on the N-substituent of the cyanurate. Substituting the bismelamine calix[4]arenes with a variety of functional groups enables the formation of assemblies in which functionalities are gathered around a box-like cavity. Mixing these homomeric assemblies creates a dynamic combinatorial library of heteromeric assemblies.

INTRODUCTION

During the last decade self-assembly has emerged as a tool that enables relatively easy access to molecular assemblies of high molecular weight and nanoscopic dimensions[1]. The elegance of self-assembly lies in the fact that the extent of *covalent* synthesis is reduced to the level of the individual components or modules, that contain information necessary for the formation of the assembly. Like Nature, chemists employ noncovalent, reversible interactions for the recognition of the modules, for instance hydrogen bonding[2] or metal-ligand interactions[3]. The advantage of using this kind of reversible interactions over irreversible covalent interactions is that it allows for 'self-correction' since the assembly is at thermodynamic equilibrium. A large variety of assemblies based on noncovalent interactions has been reported over the past decade illustrating how the concept of self-assembly has triggered the creativity of chemists[4].

One of our recent activities concerns the development of artificial receptors using a modular approach. Hitherto we have focused on covalent structures, based on a combination of modules like calix[4]arenes, resorcin[4]arenes and cyclodextrins[5]. With the synthesis of the holand, comprising two calix[4]arenes and two resorcin[4]arenes, we have reached the boundaries of synthetically accessible receptor molecules[6]. To eliminate the elaborate syntheses and to create more flexibility in the receptor molecules we recently started a research program that should lead us towards *functional self-assembled aggregates*. Here we describe our recent achievements so far in this area.

SYNTHESIS AND CHARACTERIZATION OF HYDROGEN BONDED BOX-LIKE ASSEMBLIES

Complementary hydrogen bonding between cyanuric acid and melamine has received considerable attention as a structural motif for self-assembly. Work from the groups of Whitesides[7] and Lehn[8] has shown that the recognition between these components can be used to form different types of aggregates, either lineair or crinkled *tapes*, or cyclic *rosettes*. Which type of aggregate is formed critically depends on the extent of preorganization of the complementary binding units and on steric interactions between their substituents. Due to the facile synthesis and the high degree of controllability we have decided to use this recognition motif for the self-assembly of hydrogen bonded box-like assemblies[9, 10].

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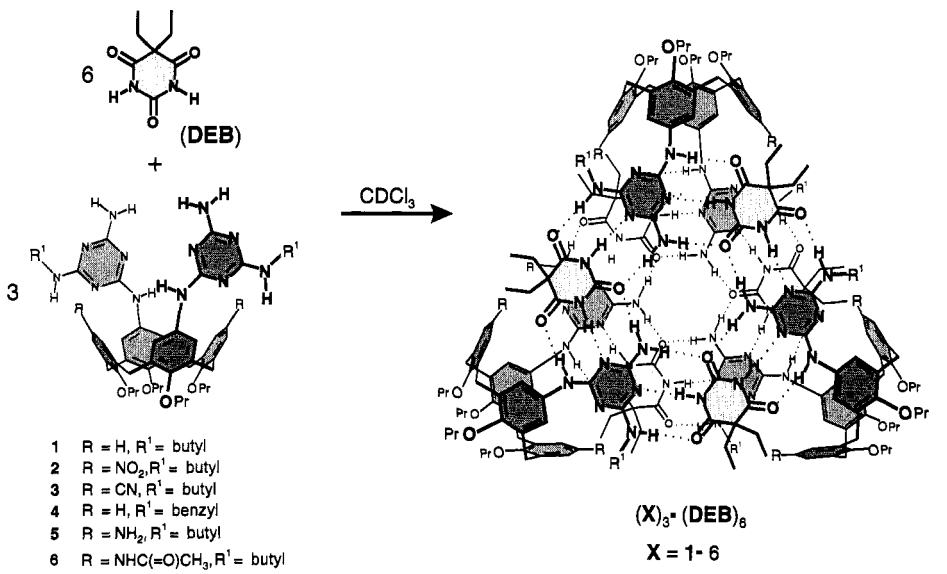

Fig. 1 Bismelamine calix[4]arenes and **DEB** form a self-assembled aggregate

Calix[4]arene **1**, diametrically substituted at the upper rim with two melamine units, spontaneously forms a well-defined box-like assembly in the presence of two equivalents of 5,5-diethylbarbiturate (**DEB**) (Fig. 1). The assembly comprises three calix[4]arenes and six diethylbarbiturates and is held together by a total number of 36 hydrogen bonds. The top and bottom of this box-like assembly consist of a cyclic hydrogen bonded platform whereas the calix[4]arene units act as side walls. The assembly is stable in apolar solvents like chloroform and toluene even at 10^{-4} M, but the stability significantly decreases when significant amounts (10-20%) of polar solvents (like DMSO and methanol). Characterization of assemblies of this type is not straightforward and structural proof is in general provided by a combination of several different techniques. Here we will discuss the use of ^{1}H NMR, X-ray spectroscopy and MALDI-TOF mass spectrometry for the structure determination of the assembly $(\mathbf{1})_3\cdot(\mathbf{DEB})_6$.

^{1}H NMR spectroscopy

Titration of bismelamine **1** with **DEB** in $CDCl_3$ shows several characteristic features (Fig. 2). Already at low concentrations of **DEB** two signals become evident at very low field. These resonances, which remain at δ = 14.10 and 13.32 regardless of the **1**:**DEB** ratio, are assigned to the hydrogen bonded NH protons of **DEB** in the complex. These protons are observed at different chemical shifts as a result of the unsymmetrical substitution of the melamine units, which gives both protons a chemically different environment in the complex. When the amount of **DEB** is increased, the signal corresponding to the NH_2 protons of free **1** decreases in intensity but remains at the same position. At the same time, two signals are observed around δ = 6.9 (c) and 6.7 (d) for both the NH_2 protons. Two additional signals appear at δ = 8.37 (e) and 7.43 (f), which correspond to the two secondary amine protons of **1** in the hydrogen bonded complex. The aromatic protons ortho to the melamine substitutents of calix[4]arene **1** give rise to signals at δ = 7.15 (g) and 6.03 (h). In free **1** these protons display broad signals at δ = 6.65-6.05. The resonance at δ = 6.03 is in accordance with a *pinched cone* structure in which the two melamines approach each other.

At a ratio of **1**:**DEB** of 1:2 the spectrum is sharp, which indicates the absence of free **1**. The 1:2 ratio is consistent with the box-like assembly that is represented in Fig. 1. When more than two equivalents of **DEB** are added, the signal for the NH protons of free **DEB** is observed alongside the two signals for the hydrogen bonded **DEB**. This indicates that exchange between hydrogen bonded and free **DEB** is slow on the NMR time scale.

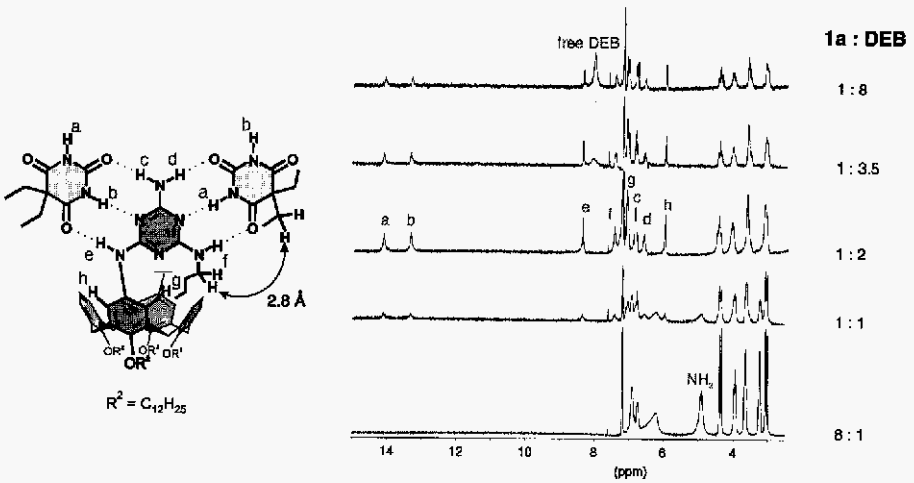

Fig. 2 Titration of bismelamine **1** with **DEB**

Single crystal X-ray diffraction studies

Upon recrystallization from toluene the assembly $(\mathbf{2})_3$•$(\mathbf{DEB})_6$ (R = NO_2) forms large single crystals. The X-ray structure, which is shown in Fig. 3, provides the first crystallographic information for this type of molecular boxes. The structure shows that the calix[4]arene units are fixed in a *pinched cone* conformation, which is the only conformation that allows simultaneous participation of the calix[4]arene units in both rosette motifs. The two rosettes tightly stack on top of each other with an interatomic separation of 3.5 Å at the edges to 3.2 Å in the centre of the box, which leaves little space for guest molecules. Interestingly, the structure reveals that the two rosette motifs are oriented in an *anti-parallel* fashion (see also Fig. 1), which means that the assembly is *stereogenic*.[11]

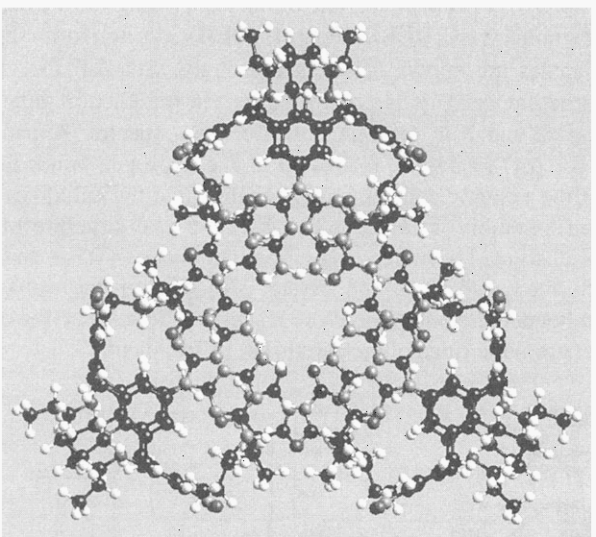

Fig. 3 X-ray crystal structure of assembly $(\mathbf{2})_3$•$(\mathbf{DEB})_6$ (topview)

2D ^{1}H NMR spectroscopy

Evidence for the fact that the solid state structure resembles the structure in solution was obtained by measuring the distances between the relevant protons in the box-like assembly with 2D NOESY experiments using the initial rate approximation. The distances are slightly larger than those observed in the crystal structure, but still provide sufficient evidence for the proposed assembly structure. A particularly strong NOE connectivity was observed between the NCH_2 protons of **2** (R = NO_2) and one of the ethyl-CH_2 groups of **DEB**. The interatomic distance of these protons *within one single* rosette is too large (*ca.* 6.4 Å) to cause the observed NOE connectivity. Therefore, it must arise from a proximity effect between the two rosette motifs, which consequently puts a limit to their mutual orientation. In the *anti-parallel* orientation (also observed in the solid state) the two protons are 2.8 Å apart, which is in perfect agreement with the strong NOE observed. The presence of this NOE connectivity provides strong evidence for the fact that the structure in solution closely resembles the solid state structure as determined by X-ray crystallography.

MALDI-TOF mass spectrometry

Additional evidence for the self-assembly of these structures was obtained by using a novel MALDI-TOF mass spectrometry technique using Ag^+ labelling[12]. The technique makes use of the high affinity of silver cations for a variety of aromatic π-donors and cyano groups. It provides for a nondestructive way to generate positively charged hydrogen bonded assemblies that can easily be detected by MALDI-TOF mass spectrometry. A sample prepared by stirring assembly $(\mathbf{3})_3.(\mathbf{DEB})_6$ with 1.5-2.0 equivalents of silver trifluoroacetate shows an intense signal at *m/z*=4220.0 (calcd. for $^{13}C_2{}^{12}C_{214}H_{282}N_{54}O_{30}.Ag^+$-complex: 4221.9) in the MALDI-TOF mass spectrum. Signals corresponding to partially formed aggregates or higher oligomers are not observed in the mass spectrum. Formation of the silver complex of assembly $(\mathbf{3})_3.(\mathbf{DEB})_6$ must result from coordination of a silver cation to one of the cyano groups, since neither $(\mathbf{1})_3.(\mathbf{DEB})_6$ nor $(\mathbf{2})_3.(\mathbf{DEB})_6$ shows any significant signal between *m/z* 1500 and 8000 in the corresponding MALDI-TOF mass spectrum.

π-Donors can be used as well for the complexation of Ag^+ which is illustrated by the fact that samples prepared by stirring assembly $(\mathbf{4})_3.(\mathbf{DEB})_6$ with $AgCF_3COO$ give a strong signal at *m/z*=4278.3 (calcd. $^{13}C_2{}^{12}C_{226}H_{276}N_{48}O_{30}.Ag^+$-complex: 4276.1) in the MALDI-TOF spectrum. Presumably the silver cation is complexed between the benzyl substituent and one of the phenyl rings of the calix[4]arene (Fig. 4). It is quite remarkably that assemblies $(\mathbf{1})_3.(\mathbf{DEB})_6$ and $(\mathbf{2})_3.(\mathbf{DEB})_6$ do not form stable Ag^+ complexes by themselves, since calix[4]arenes are known to interact strongly with Ag^+ ions through the aromatic π faces at the upper rim of the cavity. This is confirmed by the presence of intense signals for the Ag^+ complexes of calix[4]arenes **2** and **3** in the MALDI-TOF mass spectra. Apparently, the calix[4]arene skeleton loses its affinity for Ag^+ ions upon formation of the hydrogen bonded assembly. This is most probably a consequence of the extreme conformational change that the calix[4]arene skeleton undergoes when the hydrogen bonded assembly is formed. The X-ray crystal structure of assembly $(\mathbf{2})_3.(\mathbf{DEB})_6$ reveals that the melamine-substituted aromatic ring carbon atoms are 4.05 Å apart, which is 0.75 Å less than the optimal distance measured from the crystal structure of the calix[4]arene-Ag^+ complex. Formation of the hydrogen bonded assembly therefore leaves too little space for complexation of the Ag^+ ions in between the parallel aromatic rings of the calix[4]arene fragment.

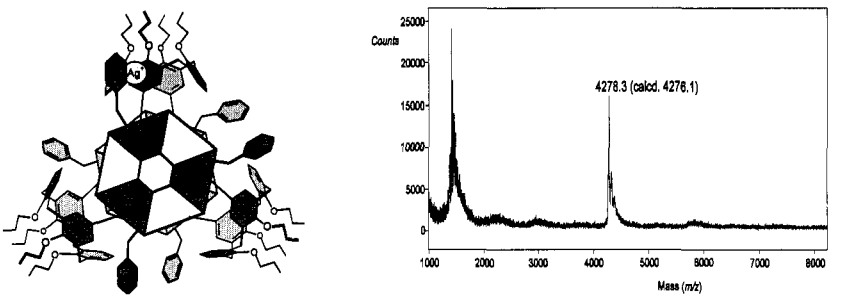

Fig. 4 Ag^+ complexation between π-donors and resulting MALDI-TOF spectrum

From these results it can be concluded that this MALDI-TOF-MS technique after Ag^+ labeling is a convenient new tool for the mass spectrometric characterization of hydrogen bonded assemblies. The absence of any signal corresponding to fragments of assemblies in the mass spectrometer illustrates the unprecedented mildness of the technique. The method requires only a binding site for the soft Ag^+ ion in order to charge the noncovalent assembly in a nondestructive way. Aromatic π-donors, which can sandwich a Ag^+ ion, or cyano groups are adequate for this purpose, but in principle many other functionalities such as acetylenes, ethylenes, amines, and sulfur groups may interact strongly with Ag^+ ions.

CONFORMATIONAL ISOMERISM OF HYDROGEN BONDED ASSEMBLIES

In assembly $(\mathbf{1})_3.(\mathbf{DEB})_6$ the two melamines on each calix[4]arene are in an anti-parallel orientation with respect to each other and this conformational isomer is therefore referred to as the staggered conformer. Two other conformers of the assembly are possible as well in which the melamines on each calix[4]arene unit are facing the same side of the calix[4]arene (Fig. 5), *i.e.* the symmetrical eclipsed and the unsymmetrical eclipsed (Fig. 6). In both assemblies the two rosette motifs are aligned on top of each other. The difference between these two eclipsed conformers arises from the different positions of the calix[4]arene components in the assembly. In the symmetrical eclipsed conformer all calix[4]arenes 'face' the same direction, yielding a C_3 symmetrical assembly. In the unsymmetrical eclipsed conformer, one of the three calix[4]arenes is oriented in an opposite direction compared to the other two, resulting in a C_1 symmetrical assembly. For the C_3 symmetrical conformers (staggered or symmetrical eclipsed) two ^1H NMR signals are expected for the imide protons of the cyanurate, for reasons given before. In the C_1 symmetrical conformer (unsymmetrical eclipsed) all imide protons of the cyanurates within a single rosette are in a different chemical environment and the assembly should therefore exhibit six different signals in the 13-15 ppm region.

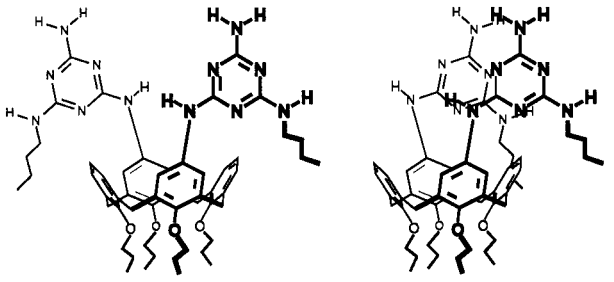

Fig. 5 Staggered and eclipsed orientation of melamine units

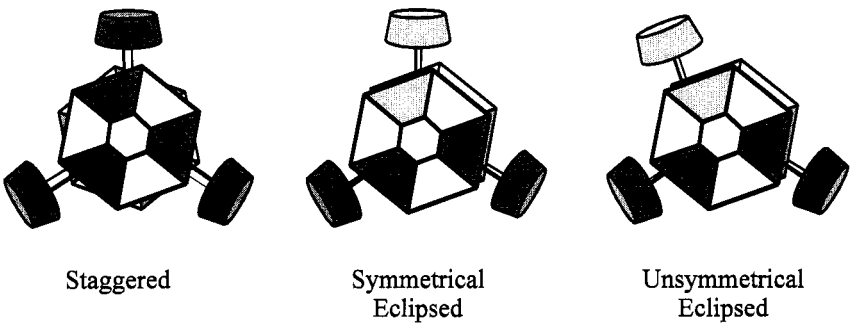

Fig. 6 Schematic representation of the possible conformational isomers

Assemblies which contain diethylbarbiturate as the complementary compound show in all cases only two imide proton signals in the ^{1}H NMR spectrum, which, according to 2D NMR techniques, belong to the staggered conformer (*vide supra*). However, the ^{1}H NMR spectrum of assembly $(\mathbf{1})_3.(\mathbf{CYA1})_6$ (Fig. 7) appears to be much more complicated[13,14]. In the diagnostic region at 13-15 ten peaks are observed for $(\mathbf{1})_3.(\mathbf{CYA1})_6$ instead of the two signals observed for $(\mathbf{1})_3.(\mathbf{DEB})_6$ (Fig. 8). A detailed 2D ^{1}H NMR study revealed that these signals originate from the staggered (●), symmetrical eclipsed (■) and unsymmetrical eclipsed (□) conformers.

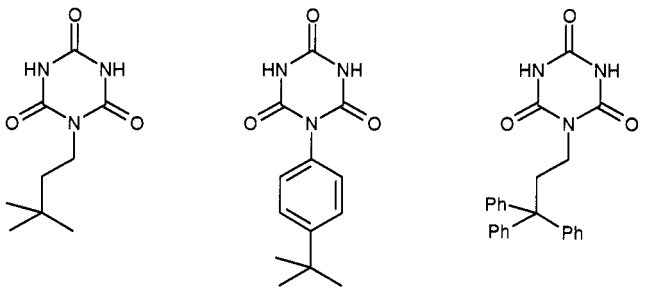

Fig. 7 Cyanurates

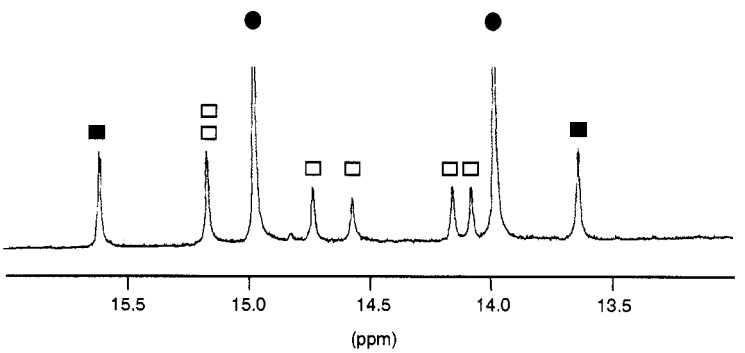

Fig. 8 Part of the ^{1}H NMR spectrum of assembly $(\mathbf{1})_3(\mathbf{CYA1})_6$. Ten signals are observed originating from the staggered (●), symmetrical eclipsed (■) and unsymmetrical eclipsed (□) conformer (two signals coincide)

Apparently the assembly process is not so well-defined when neohexylcyanurate is used instead of diethylbarbiturate. The reason for the exclusive formation of the staggered conformer with diethylbarbiturate is likely to be steric, but the influence of electronic factors cannot be excluded. In the eclipsed conformers the barbiturates in upper and lower rosette would be aligned on top of each other causing a steric hindrance of the ethyl chains. Since in neohexylcyanurate the sp^3 hybridized carbon is replaced by a sp^2 hybridized nitrogen the neohexyl substituent is oriented in the plane of the rosettes thus imposing a different steric effect on the assembly. In this case it is sterically possible to form the eclipsed conformers as well. Furthermore, the higher electronegativity of nitrogen compared to carbon causes the cyanurates to form stronger hydrogen bonded complexes with melamines[15] and might also favor the formation of the eclipsed conformers.

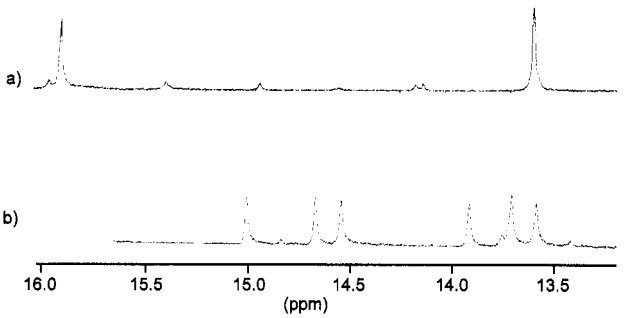

Fig. 9 Part of the ^{1}H NMR spectra of assemblies (a) $(\mathbf{1})_3(\mathbf{CYA2})_6$ and (b) $(\mathbf{2})_3(\mathbf{CYA3})_6$

Further studies were carried out to determine if this behavior is a general phenomenon for *N*-substituted cyanurates. The results showed that the influence of the cyanurate substituents on the conformer distribution is difficult to predict. For instance, the ^{1}H NMR spectrum of assembly $(\mathbf{1})_3$.**(CYA2)** shows two major peaks in the 13-16 ppm region together with 6 smaller signals, the latter accounting for about 10% of the total aggregate present (Fig. 9a). The 6 signals are assigned to the unsymmetrical eclipsed conformer, but the two major signals can in principle originate from either the staggered or symmetrical eclipsed conformer.

To illustrate that the assembly process sometimes gives surprising results, part of the ^{1}H NMR spectrum of the assembly $(\mathbf{2})_3$.$(\mathbf{CYA3})_6$ is depicted in Fig. 9. In this case only the 6 signals belonging to the unsymmetrical eclipsed conformer are observed. At this moment rationalization of this result has not been successful, demonstrating that the assembly process has not yet been comprehended to every extent. Most likely a combination of steric and electronic factors accounts for the difference in assembly behavior of cyanurates compared to diethylbarbiturate.

FUNCTIONAL GROUP DIVERSITY IN HYDROGEN BONDED ASSEMBLIES

In the hydrogen bonded assembly *six* functionalizable sites R (see Fig. 1) are gathered around the box-like cavity. In view of our objective to generate functional group diversity in or around non-covalently assembled cavities, we studied how the nature of the functionality at position R affects the stability of such calix[4]arene box-like assemblies in solution[10].

The introduction of polar substituents at positions R, such as nitro or cyano, does not influence the stability of the cyclic hydrogen bonded assembly in solution to any significant extent. Compounds **2** (R= NO_2) and **3** (R= CN) readily assemble in chloroform in the presence of **DEB**, the ^{1}H NMR spectra of which are virtually identical to that of $(\mathbf{1})_3$•$(\mathbf{DEB})_6$ (R= H). Titration of **3** (R= CN) with **DEB** clearly proved the 3:6 stoichiometry of the box-like assembly formed.

Surprisingly, the stability of assembly $(\mathbf{5})_3$•$(\mathbf{DEB})_6$ (R= NH_2) is highly solvent dependent. The ^{1}H NMR spectrum in toluene-d_8 is very well-defined and shows two singlets at 14.55 and 13.85 ppm for the magnetically nonequivalent barbiturate NH protons. In $CDCl_3$, however, the spectrum is very broad and does not show any resonance in the region between 13 and 15 ppm, which indicates a preference for non-specific oligo- or polymer formation in this solvent. The decreased stability of $(\mathbf{5})_3$•$(\mathbf{DEB})_6$ in the more polar solvent $CDCl_3$ is most probably related to the hydrogen bond donating ability of the two NH_2 groups.

Compound **6** [R= $NHC(O)CH_3$] does not form the box-like assembly in either $CDCl_3$ or toluene-d_8. Both ^{1}H NMR spectra exhibit broad resonances indicating non-specific aggregation. Also in this case the formation of intramolecular hydrogen bonds, *i.e.* between the amide carbonyl and the melamine NH proton, seems to be primarily responsible for inhibiting the assembling ability of **5**.

Towards dynamic combinatorial libraries

Combinatorial chemistry allows for the simultaneous synthesis of large libraries of structurally well-defined molecules. These libraries are prepared by statistical combination of reactive molecular fragments *via* the irreversible formation of covalent bonds. In principle, one could also use noncovalent interactions, like hydrogen bonding, to build in a reversible way libraries of small complementary molecules[16]. In the previous section it was demonstrated that a large variety of functional groups can be accumulated in a hydrogen bonded assembly.

Mixing homomeric assemblies N, carrying different functional groups should theoretically result in the formation of a mixture of heteromeric assemblies, M. This provides a rapid method to create a large number of assemblies at thermodynamic equilibrium and can be regarded as the build up of a dynamic combinatorial library.[17] The total number of assemblies P (*i.e.* $N + M$) present in such a library rapidly increases with increasing N following equation (1).

$$P = N + N(N\text{-}1) + [N(N\text{-}1)(N\text{-}2)]/6 \quad (1)$$

For the smallest possible library (N=2, P=4) we have studied the combination of assemblies **(1)$_3$.(DEB)$_6$** and **(2)$_3$.(DEB)$_6$**. The four possible assemblies are schematically depicted in Fig. 10.

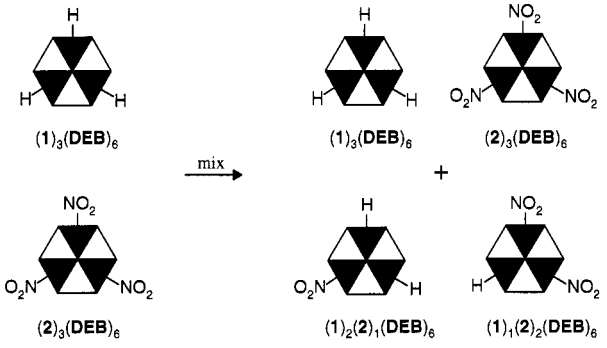

Fig. 10 Self-assembled combinatorial library

Mixing of 5 mM solutions of **(1)$_3$.(DEB)$_6$** and **(2)$_3$.(DEB)$_6$** at 0 °C (ratio 2:1) in toluene-d_8 gives only a mixture of the two separate homomeric assemblies. Exchange of the bismelamine calix[4]arenes is extremely slow at this temperature and, as a consequence, formation of the heteromeric assemblies is not observed. When the mixture is warmed to temperatures over 15 °C the heteromeric assemblies start to form. After 2.5 h at 25 °C the system reaches the thermodynamic equilibrium. (Fig. 11).

The unsymmetrical heteromeric rosettes **(1)$_2$(2)$_1$.(DEB)$_6$** and **(1)$_1$(2)$_2$.(DEB)$_6$** cause multiple signals in the characteristic 13-15 ppm region. Signals of all four assemblies could be assigned with 2D NMR measurements. The relative concentrations were 1:3:3:1, in agreement with a statistical distribution. The complex ^{1}H NMR spectrum for this small library shows that ^{1}H NMR spectroscopy might not be the appropriate technique for analyzing larger dynamic libraries. Therefore characterization was also performed with Ag^+ assisted MALDI-TOF mass spectrometry as described previously. Individual solutions of the assemblies, pretreated with 1.5 equiv. of CF_3CO_2Ag in chloroform, give intense signals corresponding to **(1)$_3$.(DEB)$_6$.Ag$^+$** and **(2)$_3$.(DEB)$_6$.Ag$^+$** respectively. The mixture of **(1)$_3$.(DEB)$_6$** and **(2)$_3$.(DEB)$_6$** on the other hand shows two additional signals for the heteromeric assemblies. Especially for the characterization of libraries with more components, mass spectrometry will be an important tool.

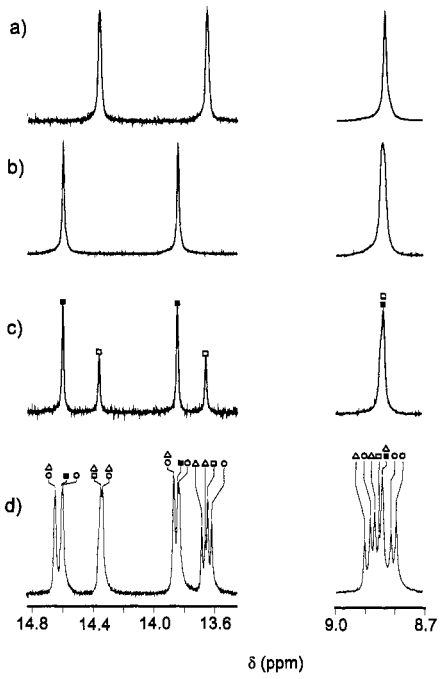

Fig. 11 Temperature dependent formation of heteromeric assemblies as observed with ^{1}H NMR. Shown are the imide proton signals and one NH signal of the bismelamine of a) homomeric assembly $(\mathbf{1})_3.(\mathbf{DEB})_6$, b) homomeric assembly $(\mathbf{2})_3.(\mathbf{DEB})_6$, c) 2:1 mixture of $(\mathbf{1})_3.(\mathbf{DEB})_6$ and $(\mathbf{2})_3.(\mathbf{DEB})_6$ at 0 °C and d) 2.5 h after mixing $(\mathbf{1})_3.(\mathbf{DEB})_6$ and $(\mathbf{2})_3.(\mathbf{DEB})_6$ at 25 °C.

CONCLUSIONS

Here we have presented our achievements in creating functional hydrogen bonded assemblies. Characterization of these dynamic assemblies was performed by ^{1}H NMR spectroscopy, single crystal X-ray diffraction and MALDI-TOF mass spectrometry technique with Ag^+ labelling. From these studies it appeared that the **DEB**-containing assemblies are stereogenic, due to an anti-parallel orientation of the rosette motifs. However, other conformers are observed as well when N-substituted cyanurates were used to form rosettes instead of **DEB**. Furthermore, the possibility of bringing different functional groups together in a dynamic assembly was demonstrated. The possibility of creating heteromeric assemblies by mixing homomeric assemblies provides a new strategy that enables the noncovalent synthesis of a dynamic library of potential receptor molecules. Currently, we are actively pursuing the use of modified assemblies as receptor molecules for guests.

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